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Phosphite-mediated conversion of benzaldehydes into stilbenes via umpolung through a dioxaphospholane intermediate



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ABSTRACT

The phosphite-mediated coupling of two benzaldehydes into 2,2,2-triethoxy-1,3,2-dioxaphospholanes was investigated using ^{13}C NMR spectroscopy and was found to be very sensitive to the nature of the *ortho/para* substituents, and promoted by electron-withdrawing groups (EWGs). Stilbene-extended tetrathiafulvalenes were prepared by heating the intermediate dioxaphospholane, containing aldehyde substituents at *para* positions and ethynyl groups at *ortho/meta* positions, with 1,3-dithiol-2-thiones in $\text{P}(\text{OEt})_3$. While EWGs promoted dioxaphospholane formation, electron-donating groups (EDGs), generated by conversion of the aldehydes into dithiafulvenes, promoted subsequent conversion into an alkene.

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The phosphite-mediated coupling of 1,3-dithiol-2-chalcogenones is a key reaction for the formation of derivatives of tetrathiafulvalene (TTF),¹ a redox-active molecule which has generated significant interest in both materials and supramolecular chemistries.² Serendipitously, we found that this reaction could also be used to prepare extended TTFs **1** and **2** (Fig. 1), which were coined 'H-Cruciforms' on account of the molecular shape of the central part.³ These compounds were prepared from an acetylenic derivative **5** of terephthalaldehyde and the 1,3-dithiol-2-thiones **3**⁴ and **4**,⁴ respectively. Thus, not only had **3** or **4** reacted with an aldehyde functionality of the terephthalaldehyde, but more importantly, two aldehyde functionalities had coupled together under the influence of triethyl phosphite to furnish a carbon–carbon double bond as part of a stilbene moiety. Interestingly, from terephthalaldehyde itself, we only isolated the extended TTF where each aldehyde group had reacted with a 1,3-dithiol-2-thione. Ramirez et al.⁵ have shown that *o*- and *p*-nitrobenzaldehyde, that is, aldehydes with electron-withdrawing substituents, can react with trialkyl phosphites at 20 °C to generate 2,2,2-trialkoxy-1,3,2-dioxaphospholanes, and we hypothesize that such heterocyclic compounds could be intermediates in the formation of stilbenes **1** and **2**. To investigate this carbon–carbon bond forming reaction in further detail, we decided to study the outcome of subjecting a variety of substituted benzaldehydes to reactions with triethyl phosphite.

First, we examined the reaction between triethyl phosphite and terephthalaldehyde at 100 °C—these experiments were performed in neat phosphite in an NMR tube with a $\text{DMSO}-d_6$ insert tube, while recording ^{13}C NMR spectra at regular intervals. ^{13}C NMR spectroscopic analysis of the reaction mixture revealed the disappearance of the starting material and the appearance of multiple new signals in the aromatic region and two new signals at 79 and 74 ppm, assigned to the carbon atoms of the five-membered dioxaphospholane ring (*cis* and *trans* isomers; however, we were unable to make an absolute assignment). The two remaining aldehyde groups were not converted. A similar outcome was observed with 4-nitrobenzaldehyde. The reactivity of terephthalaldehyde and 4-nitrobenzaldehyde toward phosphite encouraged the investigation of the reaction in different solvents. Gratifyingly, we found that the reaction proceeded in MeCN, CH_2Cl_2 , THF, and toluene at room temperature with 5–10 equiv of $\text{P}(\text{OEt})_3$. In the case of toluene, heating to 40–60 °C increased the reaction rate substantially; in the cases of THF, CH_2Cl_2 , and MeCN, ambient temperature was sufficient to affect the transformations (in agreement with the results of Ramirez et al.⁵ in CH_2Cl_2). With 4-nitrobenzaldehyde, the transformation performed in MeCN at rt was virtually complete by the time the ^{13}C NMR spectrum had been recorded (within 10 min), employing two molar equivalents of $\text{P}(\text{OEt})_3$ (Fig. 2). The screening of different molar equivalents of $\text{P}(\text{OEt})_3$ showed that the transformation could be driven to completion with just 0.5 molar equivalents in the case of 4-nitrobenzaldehyde. The reaction rate increased dramatically, however, when an excess of $\text{P}(\text{OEt})_3$

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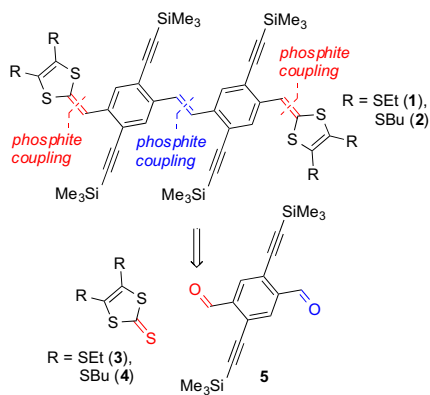
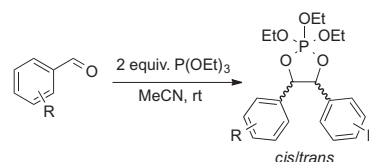


Figure 1. H-Cruciform extended TTFs—prepared by phosphite-mediated couplings.

was present. The reaction was also easily performed on preparative scale from which we isolated 2,2,2-triethoxy-4,5-bis(4-nitrophenyl)-1,3,2-dioxaphospholane in a yield of 97% (see the [Supplementary material](#)).

Our next objective was to study dioxaphospholane formation in MeCN using two equivalents of $P(OEt)_3$ and a variety of benzaldehyde derivatives, as shown in [Scheme 1](#) and [Table 1](#). The degree of conversion was estimated by comparing key ^{13}C NMR signals in the dioxaphospholane and in the starting material. Since signal intensities in ^{13}C NMR spectroscopy cannot be quantitatively compared, the conversion is formulated in a very conservative manner; that is, in cases where no starting material is observed, the conversion is reported as >95% (only very minor signals from unidentified by-products are present). As can be seen from [Table 1](#), the balance for the outcome of the reaction is very subtle. First of all, we do not observe conversion of benzaldehyde itself (entry 1); only starting material was observed. It can be seen that electron-withdrawing groups (EWGs) such as NO_2 , CHO in *ortho* or *para* positions (entries 2, 3, 5 and 6) favor the formation of the dioxaphospholane, in each case, as a mixture of *cis* and *trans* isomers. However, other electron-withdrawing *para* substituents such as F, I, and CF_3



Scheme 1. Formation of dioxaphospholanes from substituted benzaldehydes (for details, see [Table 1](#)).

Table 1
Aldehydes tested for dioxaphospholane formation (see [Scheme 1](#))

| Entry | Reactant (substituent R) | Dioxaphospholane ^a | Time |
|-------|--|-------------------------------|----------------------|
| 1 | H | None | 14 d ^b |
| 2 | <i>p</i> -O ₂ N | >95% ^c | <10 min |
| 3 | <i>o</i> -O ₂ N | >95% ^c | <30 min |
| 4 | <i>m</i> -O ₂ N | None | 14 d ^b |
| 5 | <i>o</i> -CHO | >95% ^c | 2 h |
| 6 | <i>p</i> -CHO | >95% ^c | 2 h |
| 7 | <i>p</i> -CO ₂ Me | 15–20% | 14 d ^b |
| 8 | <i>p</i> -CN | 80–90% | 36–48 h ^d |
| 9 | C(O)Me | 15–20% | >72 h |
| 10 | <i>p</i> -F | None | 14 d ^b |
| 11 | <i>p</i> -I | None | 14 d ^b |
| 12 | <i>p</i> -F ₃ C | None ^e | 14 d ^b |
| | carbonyl reactant | | |
| 13 | <i>p</i> -O ₂ NC ₆ H ₄ CH=CHCHO | None | 14 d ^b |
| 14 | 5 | >95% ^{c,f} | 4 h |
| 15 | <i>p</i> -O ₂ NC ₆ H ₄ C(O)Me | None | 14 d ^b |

^a Estimated conversion into dioxaphospholane as determined by ^{13}C NMR (126 MHz, DMSO-*d*₆) spectroscopy.

^b No conversion observed after 14 d at 80 °C.

^c No aldehyde ^{13}C NMR signal remained.

^d Reaction was performed in refluxing MeCN.

^e Reaction was performed in neat $P(OEt)_3$, due to solubility issues.

^f The product contained mainly one of the isomers.

(entries 10–12) do not favor the formation of the dioxaphospholane. After prolonged exposure to $P(OEt)_3$, new signals began to appear, but they were not consistent with dioxaphospholanes.

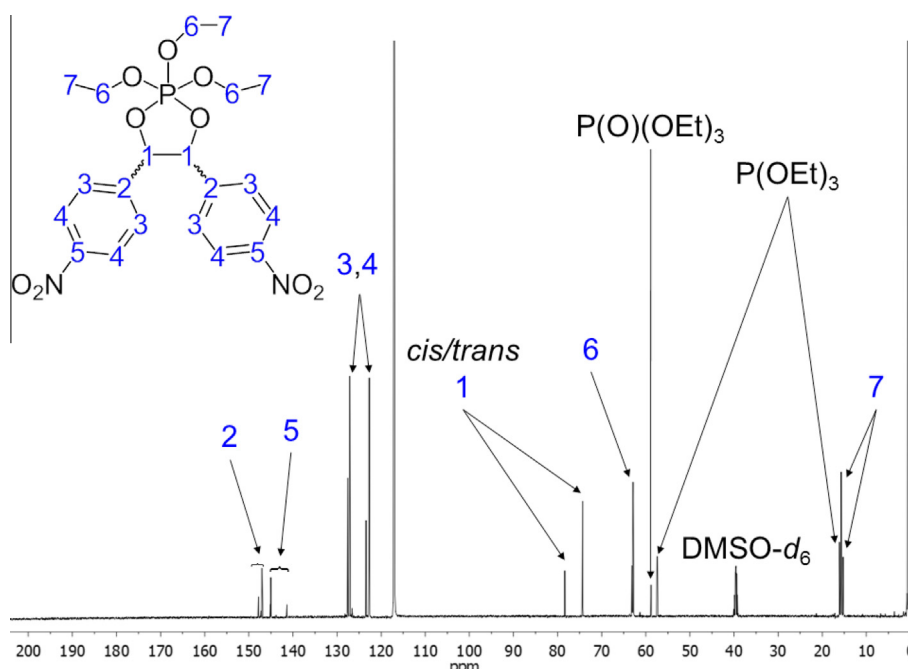
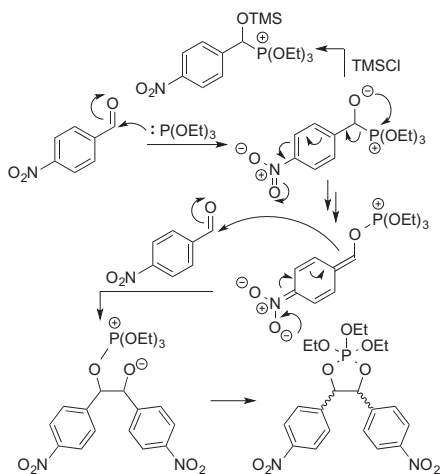


Figure 2. ^{13}C NMR (126 MHz, DMSO-*d*₆) spectrum of the reaction mixture obtained from heating 4-nitrobenzaldehyde with 2 equiv of $P(OEt)_3$ in MeCN. Signals split due to the presence of *cis/trans* isomers. As can be seen, no aldehyde resonance remained in the region around 190 ppm, and all the signals could be accounted for.

Our observations are in line with those of Ramirez et al.⁵ who found that *p*-Cl-, *p*-MeO-, *p*-MeCO(NH)-benzaldehydes, benzaldehyde itself, and furfural did not react with neat P(OEt)₃ at 100 °C for 48 h, while some reaction was observed for *m*-O₂N-benzaldehyde after 8 h. With a *p*-CN substituent we found that the conversion into the dioxaphospholane proceeded very slowly at rt, but in refluxing MeCN, the reaction was complete in less than 48 h. A C(O)Me substituent still favored formation of the dioxaphospholane, but the reaction proceeded even slower than that with the CN substituent. Notably, the ketone unit was untouched in the reaction. The CO₂Me substituent showed very slow formation of dioxaphospholane (entry 7); at elevated temperature, it went faster and ca. 20% of the dioxaphospholane was observed after 24 h at 80 °C. Compound **5** underwent conversion into the dioxaphospholane reasonably fast (entry 14), being unhindered by the alkynyl substituents. However, where all the other dioxaphospholanes were obtained as *cis/trans* mixtures, only one isomer was favored for this compound, tentatively assigned as the *trans* isomer. This could be due to the steric constraints imparted by the trimethylsilyl ethynyl substituents. In accordance with the experiments performed on 4-formylacetophenone (entry 9), 4-nitroacetophenone was unreactive toward P(OEt)₃ (entry 15); only starting material was observed in the ¹³C NMR spectrum. Changing the solvent to CH₂Cl₂, THF, or toluene did not result in conversion either.

We suggest a mechanism for dioxaphospholane formation as outlined in Scheme 2, with initial attack of phosphorus on the carbonyl carbon. This assumption is supported by experiments in which a capping reagent is added. Thus, upon the addition of trimethylsilylchloride (TMSCl), the TMS-protected alcohol was formed (Scheme 2). The ¹³C NMR resonance around 71 ppm was split into a doublet by coupling to the neighboring phosphorus, with a ¹J coupling of ≈157 Hz, in agreement with J_{C-P} coupling constants observed in a study by Zhou et al.⁶ A related species was obtained by reacting benzaldehyde with P(OEt)₃ in the presence of TMSCl.

Our next objective was to investigate the potential of the dioxaphospholanes to act as precursors for stilbenes. Heating with excess phosphite was thus attempted, but no stilbenes were observed by ¹H or ¹³C NMR spectroscopy or GC–MS. After 5 days at 80–100 °C, however, some epoxides seemed to have formed based on the appearance of new carbon resonances around 60 ppm. We note that formation of small amounts of stilbene was previously observed when heating benzaldehyde in P(OEt)₃ at 220 °C in an ampoule for 8.5 h, as was the formation of difuryl ethylene by heating furfural and P(OEt)₃ at 160 °C.⁷

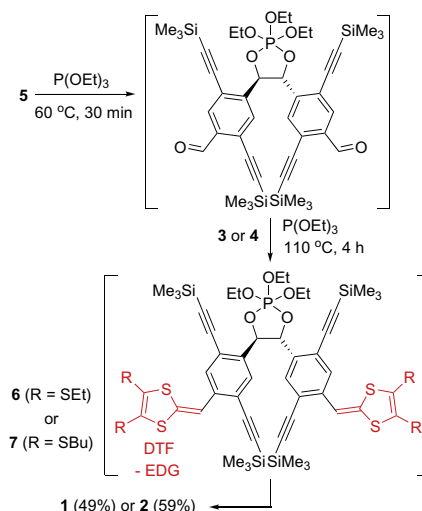


Scheme 2. Proposed mechanism for the formation of the dioxaphospholane, illustrated with 4-nitrobenzaldehyde as the substrate and trapping of the intermediate with TMSCl.

In order to elucidate the role of a dioxaphospholane intermediate in the formation of the H-Cruciforms, the dioxaphospholane was first formed from **5** in P(OEt)₃, and was then treated with the 1,3-dithiol-2-thiones **3** and **4** (1.25 equiv per aldehyde moiety), as illustrated in Scheme 3. This procedure furnished the H-Cruciform products **1** and **2**,⁸ showing that the dioxaphospholane can indeed act as an intermediate for the formation of a carbon–carbon double bond when the end-groups are changed to electron-donating groups (EDGs), assuming that dithiafulvene (DTF) compounds **6** and **7** are intermediates. Performing the reaction in this way improved the yield dramatically (from 21%³ to 49% for the SEt derivative, and from 17%³ to 59% for the SBU derivative)—relative to our previous method where **3/4** and **5** were heated together in neat P(OEt)₃. The improved yields may, to some extent, also originate from an easier work-up procedure as less phosphite was used, which meant that pouring the cold reaction mixtures into cold MeOH yielded the H-Cruciforms as fine red powders (**2** was further purified by size-exclusion chromatography on BioBeads SX-3 to remove minor impurities). Mass spectrometric (MS) analysis of the crude reaction mixture, from which H-Cruciform **2** was isolated, indicated the presence of a compound in which the central part is an epoxide rather than a double bond. We believe that epoxide formation is promoted as the electron-withdrawing CHO end-groups are converted into electron-donating DTF groups. Epoxide species with 2 DTFs or 1 DTF/1 CHO end-groups were also observed by MS analysis in another experiment (see Supplementary material), where **4** and **5** were refluxed in equimolar amounts in P(OEt)₃ and toluene (1:2 v/v), indicating that epoxides could be intermediates toward the stilbene product.

Finally, we heated equimolar amounts of terephthalaldehyde and **4** in P(OEt)₃ to give the DTF–C₆H₄–CHO product in high yield (64%, see Supplementary material).⁹ The reluctance of the remaining CHO to convert into a dioxaphospholane in the presence of an EDG (DTF) was confirmed by ³¹P- and ¹³C NMR spectroscopy after heating the compound in P(OEt)₃ for 12 h at 60 °C. This shows the advantage of first making a dioxaphospholane in the H-Cruciform synthesis.

In conclusion, dioxaphospholane formation from benzaldehydes relies on EWGs, while such groups retard the subsequent conversion into an epoxide or stilbene. A dioxaphospholane is nevertheless believed to be an intermediate in the pathway to so-called H-Cruciform molecules with the formation of a carbon–carbon double bond being a key step. Indeed, treatment of the dioxaphospholane with 1,3-dithiol-2-thiones in triethyl phosphite



Scheme 3. Improved synthesis of H-Cruciforms via a dioxaphospholane intermediate.

leads to the formation of these products in considerably better yields than those previously obtained. This improvement is particularly important for using these molecules as modules for acetylenic scaffolding (by desilylation followed by acetylenic coupling reactions), targeting redox-active macrocycles or grid-like structures. The successful conversion of the dioxaphospholane into a stilbene (presumably via an epoxide) is likely related to the phosphite-mediated conversion of *para*-substituents from EWGs (CHO) to EDGs (DTF) upon the addition of the 1,3-dithiol-2-thione. The sequential conversion of a benzaldehyde derivative into a stilbene thus relies on opposing electronic effects in the two transformations—the conversion relies on a sort of umpolung. This knowledge may allow access to a wider variety of extended TTFs using other dialdehydes as starting materials. In addition, other methods of performing the umpolung using electronically ‘tunable’ substituents should be of interest to pursue in future work.

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Supplementary data

Supplementary data (experimental procedures and ^{13}C NMR spectra and selected ^{31}P NMR spectra) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.02.108>.

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8. *Synthesis of 1*: Dialdehyde **5** (166 mg, 0.508 mmol) was dissolved in N_2 -flushed $\text{P}(\text{OEt})_3$ (3 mL), which had been dried over 4 Å molecular sieves. The resulting pale yellow solution was stirred for 1 h at 60 °C, then 1,3-dithiol-2-thione **3** (449 mg, 1.76 mmol) was added. After stirring for 4.5 h at 120 °C, the mixture was allowed to cool to rt and then poured into cold MeOH (25 mL). The mixture was left at ca. 5 °C overnight, and the resulting red precipitate was collected by filtration and washed with cold MeOH (4×15 mL), providing the product as a red powder (131 mg, 49%). Characterization data were in accordance with Ref. 3. The same procedure could be used for the synthesis of **2** from **4** and **5**. The use of size-exclusion chromatography with BioBeads SX-3 was needed here after precipitation.
9. For a related synthesis of the hexylthio-substituted analogue ($\text{R} = \text{SHex}$), see: Guo, K.; Yan, K.; Lu, X.; Qiu, Y.; Liu, Z.; Sun, J.; Yan, F.; Guo, W.; Yang, S. *Org. Lett.* **2012**, *14*, 2214–2217.